Synthesis, Characterization and Antibacterial Activity of Some New Five-Seven Membered Rings Attached to Sulfonamide Compounds

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Abstract
This work includes the synthesis of some new five-seven heterocyclic rings derived from benzenesulfonilhydrazide as starting material. Its condensation with 4-methoxy and 4-nitro benzaldehyde gives the Schiff bases (1a,b). Schiff bases were reacted with cyclic anhydrides given Oxazepine, Thiazepine derivatives(2,3,4 a,b)(seven membered ring) and with 2-mercaptop benzoic acid gives thiazine derivatives (6a,b)(six membered ring) finally with thioglycolic acid give thiazolidine ring(five membered ring) scheme(3). The synthesized compounds have been characterized by melting points, FT-IR, $^1$H-NMR spectroscopy, $^{13}$C-NMR and Elemental analysis. some of synthesized compounds were tested for their antibacterial activity against staphylococcus aureus, pseudomonous aureous and Escherichia coli. The results showed good efficacy against these types of bacteria.

Keywords: sulfonamide, Oxazepine, Thiazepine, Thiazine, Thiazolidine, Schiff bases, Antibacterial activity.
Introduction

Sulfonamide compounds or sulfonamide drugs have brought about an antibiotic revolution in medicinal chemistry are associated with a high range of biological activities [1-3]. Oxygen, Nitrogen; Sulfur heterocycles fused with sulfonamide compounds have a wide amount of attention the literature. Heterocyclic compounds attached with sulfonamides were used as carbonic anhydrase inhibitors[4,5], Antimicrobial activity[6,7], γ-secretase inhibitors[8], anti-inflammatory[9], Anticancer[10]. Thiazolidine is a type of heterocyclic compound contains five membered ring with a sulfur, nitrogen atoms. It is an important compound in medicinal chemistry because it has a wide spectrum in biological activity [11]. The thiazine nucleus has been incorporated into a wide variety of therapeutically agents such as antimicrobial[12], antibacterial[13] and cannabinoid[14]. Oxazepine compounds are seven membered ring contains oxygen and nitrogen. It has documented that oxazepines are important in the diverse fields of heteroatom chemistry and biochemistry owing to its high range of biological activities[15]. These compounds are important in medicinal chemistry because they are used as starting material for synthesis of diazepam (valum), it is a class of drug used as relaxant and muscle relaxant because it is often seen in forensic and clinical cases[16]. Heterocycles containing thiazepine fragment are a key moiety in a large number of natural and synthetic bio-active molecules. Thiazepine compounds are used as exhibited angiotensin-converting enzyme inhibition [17], Antiviral [18] and anticancer[19].

Experimental

Whilst p-nitro benzaldehyde, p-methoxybenzaldehyde, maleic anhydride, phthalic anhydride, o-sulfobenzoic acid cyclic anhydride, 2-mercapto benzoic acid, thioglycolic acid were obtained from Sigma-Aldrich. All solvents were purchased from Fluka used as received. Melting points were determined on digital stuart SMP-3 apparatus. Fourier transform Infrared spectra were measured on Schimadzu 8300 spectrophotometer using KBr disks. 1H-NMR, 13C-NMR spectra were measured in DMSO solutions on a Bruker Av spectrophotometer (300 MHz) using TMS as an internal reference (chemical shifts in δ ppm). All synthesized compounds were elemental analysis C,H,N and S on a European Elemental analyzer. Thin layer chromatography was performed on silica gel as a stationary phase, ethyl acetate as eluent.

Synthesis of benzenesulfonylhydrazide

A benzenesulfonylchloride (0.01 mol) in dry benzene and hydrazine hydrate (2 ml) were added. The mixture was stirred and heated at reflux for 3h; the reaction mixture was poured with good stirring into 100 ml ice-cold water and kept at room temperature until the reaction product separated as a solid, which was filtered off and recrystallized from ethanol, m.p= 104-1-60°C as literature.

Synthesis of N’-(4-substitutedbenzylidene)benzenesulfonylhydrazide(1a,b)

A solution of benzenesulfonylhydrazide (0.01 mol) on ethanol absolute (15 ml), the appropriate aldehyde (0.01 mol) and 2-3 drops of glacial acetic acid was refluxed for 3h. The result was allowed to cool at room temperature. The solid was collected by filtration and recrystallized from ethanol absolute to give the pure Schiff bases. The FT-IR of these compounds showed disappearance bands of (-NH₂) group and appearance bands at (1633-1639) cm⁻¹ due to of (C=N) moiety.
Synthesis of N-(3-(4-substitutedphenyl)-1,5-dioxobenzo[e][1,3]oxazepin-4(1H,3H,5H)-yl)benzenesulfonamide(2a,b).

Into a dry 50 ml round bottom flask, introduce (0.01mol) of Schiff bases in 20 ml of dry benzene and stirred the reaction mixture for 15min then refluxed at 60°C for 2h. The mixture was allowed to stand overnight and solid separated out was filtered and washed with dioxane. The compound so obtained was dried and recrystallized from appropriate solvents. Recrystallized from ethanol.

**Compound 2a**

Yield 75%, m.p=215°C: FT-IR(KBr) ν cm⁻¹: 3205(N-H), 2850-2900(C-H), 1722(C=O) lactone, 1666(C=O) lactam, 1170 and 1334(SO₂); H-NMR ppm: δ (DMSO 300MHz) 9.81 (s,1H, CH) in oxazepine ring, 7.3(s,1H,NH), 6.8-7.18(m, aromatic rings), 3.8ppm(s,3H,OCH₃); Anal.calc. for C₂₂H₁₈N₂O₆S :found:C, 61.10; H, 4.3; N,6.45; S,7.33 calc: C, 60.27; H, 4.14; N,6.39; S,7.31.

**Compound 2b**

Yield 79%, m.p=225°C: FT-IR(KBr) ν cm⁻¹: 3219(N-H), 2833-2910(C-H), 1720(C=O) lactone, 1660(C=O) lactam, 1358 and 1551(NO₂), 1172 and 1349(SO₂); Anal.calc. for C₂₁H₁₅N₃O₇S :found:C, 56.11; H, 3.12; N,9.43; S,7.15 calc: C, 55.63; H, 3.33; N,9.27; S,7.07.

Synthesis of N-(3-(4-substitutedphenyl)-1,5-dioxobenzo[e][1,3]thiazepin-4(1H,3H,5H)-yl)benzenesulfonamide(3a,b)

Equimolar amounts of schiff bases (1a,b) and 2-sulfobenzoic anhydride in 20 mol of dioxane were heated under reflux for 6h. the solid product so obtained on cooling was collected by filtration and crystallized from toluene.

**Compound 3a**

Yield 55%, m.p=248°C: FT-IR(KBr) ν cm⁻¹: 3203(N-H), 2800-2907(C-H), 1726(C=O) lactone, 1174 and 1348(SO₂, sulfonamide), 1141 and 1319(SO₂, in ring); Anal.calc. for C₂₂H₁₈N₂O₅S₂ :found:C, 54.00; H, 3.76; N,5.16; S,13.09 calc: C, 53.16; H, 3.82; N,5.90; S,13.52.

**Compound 3b**

Yield 65%, m.p=224°C: FT-IR(KBr) ν cm⁻¹: 3212(N-H), 2843-2897(C-H), 1729(C=O) lactone, 1172 and 1330(SO₂), 1151 and 1329(SO₂), 1345 and 1567(NO₂); H-NMR δ ppm: δ (DMSO 300MHz) 9.63 (s,1H, CH), 7.12(s,1H,NH), 6.87-7.77(m, aromatic rings); Anal.calc. for C₂₁H₁₅N₃O₅S₂ :found:C, 50.05; H, 3.13; N,8.41; S,13.23 calc: C, 49.08; H, 3.09; N,8.58; S,13.10.

**Synthesis of (Z)-N-(2-(4-substitutedphenyl)-4,7-dioxo-1,3-oxazepin-3(2H,4H,7H)-yl)benzenesulfonamide(4a,b)**

To dry benzene (30 ml) maleic anhydride(0.01 mol) and Schiff bases(0.01 mol) were added. The mixture was refluxed under 60°C for 3h., left to cool at room temperature. The solid product so formed was filtered off and crystallized from appropriate solvents.

**Compound 4a**

Yield 77%, m.p=192°C: FT-IR(KBr) ν cm⁻¹: 3203(N-H), 2833-2902(C-H), 1734(C=O) lactone, 1654(C=O) lactam, 1170 and 1334(SO₂); Anal.calc. for C₁₈H₁₆N₂O₆S :found:C, 56.11; H, 4.32; N,7.56; S,8.13 calc: C, 55.66; H, 4.15; N,7.21; S,8.26.

**Compound 4b**
Yield 56%, m.p=237°C: FT-IR(KBr) ν cm⁻¹:3210(N-H), 2830-2907(C-H),1730(C=O) lactone,1663 (C=O) lactam,1343 and 1561(NO₂),1169 and 1330(SO₂); Anal.calc.for C₁₇H₁₃N₃O₇S :found:C, 51.22; H, .33; N,10.76; S,8.08 calc: C, 50.62; H, 3.25; N,10.42; S,7.95.

**synthesis of N-(2-(4-substitutedphenyl)-4-oxothiazolidin-3-yl)benzenesulfonamide(5a,b).**

Schiff bases (0.01mol) was added portion wise in 5 ml of dry benzene with thioglycolic acid(0.01mol). the mixture was refluxed for 4h.the reaction mixture was poured into crushed ice and treated with sodium bicarbonate. The precipitate washed with ice water ,dried and recrystalized from appropriate solvents.

**Compound 5a**

Yield 48%, m.p=148°C: FT-IR(KBr) ν cm⁻¹:3205(N-H), 2833-2889(C-H),1645(C=O),1170 and 1334(SO₂); H-NMR δ ppm: 1H-NMR (DMSO 300MHz) 9.05 (s,1H, CH), 7.90(s,1H,NH), 7.07 -7.27(m,aromatic rings) ;13C-NMR ppm 197(C=O),176(CH,thiazolidine ring),70.16(CH₂); Anal.calc.for C₁₆H₁₆N₂O₄S₂ :found:C, 52.99; H, 4.64: N,7.89; S,17.17 calc: C, 52.73; H, 4.43: N,7.69: S,17.60.

**Compound 5b**

Yield 51%, m.p=258°C: FT-IR(KBr) ν cm⁻¹:3203(N-H), 2843-2897(C-H),1646(C=O),1173 and 1325(SO₂),1358 and 1556 (NO₂);Anal.calc.for C₁₅H₁₃N₃O₅S₂ :found:C, 48.08; H, 3.66; N,11.17; S,16.90.

**synthesis of N-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydro-2H-benzo[e][1,2]thiazin-2-yl)benzenesulfonamide(6a,b)**

A mixture of compounds (1,2) (0.01 mol) ,2-mercapto benzoic acid (0.01 mol) in 30 ml of dioxane. The mixture was refluxed for 4h. The reaction mixture was poured in crushed ice ,stirred 3 minutes and resulting solid was filtered ,dried and recrystalized from dioxan.

**Compound 6a**

Yield 63%, m.p=125°C: FT-IR(KBr) ν cm⁻¹:3201(N-H), 2843-2880(C-H),1680(C=O) lactam,1170 and 1338(SO₂); H-NMR δ ppm (DMSO 300MHz) 9.39 (s,1H, CH), 7.78(s,1H,NH), 6.8- 7.18(m,aromatic rings),4.01(s,3H,OCH₃);Anal.calc.for C₂₁H₁₈N₂O₄S₂ :found:C, 60.01; H, 4.10; N,6.34: S,15.24 calc: C, 59.14; H, 4.25: N,6.57: S,15.04.

**Compound 6b**

Yield 51%, m.p=242°C: FT-IR(KBr) ν cm⁻¹:3216(N-H), 2830-2881(C-H),1676(C=O) lactam,1173 and 1341(SO₂),1356 and 1557(NO₂);13C-NMR ppm 192(C=O),156(C-NO₂); Anal.calc.for C₂₀H₁₅N₃O₅S₂ :found:C, 55.65; H, 3.82; N,9.79; S,14.88 calc: C, 54.41; H, 3.42: N,9.52; S,14.53.

**Result and Discussion**

In this work , many compounds were synthesized by coupling of different compounds with Schiff bases afforded oxazepine,thiazepine,thiazine,thiazolidine. these compounds were prepared by the addition reactions between cyclic anhydride such as phthalic,maleic,o-sulfobenzoicacid with imine group in Schiff bases, seven membered rings are obtained The FT-IR of these compounds (2,4a,b) showed disappearance of (C=N) stretching band at (1639-1643) cm⁻¹ and appearance of bands in region (1720-1734 ) cm⁻¹ due to stretching vibration of(C=O)(lactone),(1654-1666) cm⁻¹ (C=O)(lactam)[20] . 1H-NMR of compound (2a) showed peaks at 9.81 (s,1H, CH) in oxazepine ring, 7.3(s,1H,NH), 6.8-7.18(m,aromatic...
3.8 ppm (s, 3H, OCH3). The FT-IR of compound (3a,b) showed disappearance band of (C=N) in Schiff bases and appearance of bands in (1723-1726) cm\(^{-1}\) due to stretching vibration of (C=O) in ring and another bands at (1141-1151) cm\(^{-1}\) and (1319-1329) cm\(^{-1}\) due to (-SO\(_2\)) group. The \(^1\)H-NMR of compound (3a) showed peaks at 9.63 ppm (s, 1H, CH) in seven membered ring, 7.12 ppm (s, 1H, NH), 6.87-7.77 ppm (m, aromatic rings).

The thiazolidinone derivatives (5a,b) were synthesized by refluxing mercapto acetic acid with Schiff bases in dry benzene for 4 hrs. The suggested mechanism of thiazolidinone (5a,b) were obtained as following in scheme 1.

![Scheme 1: Mechanism for the synthesis of thiazolidinone compounds](image)

The FT-IR of these compounds (5a,b) showed disappearance of imine group and appearance of new bands at (1646-1646) cm\(^{-1}\) for (C=O) in thiazolidinone ring.

Thiazine derivatives (6a,b) prepared by the heating of 2-mercaptobenzoic acid with Schiff bases in dioxane the mechanism of the reaction systematically investigated as [4+2] cycloaddition. FT-IR spectrum showed the disappearance of bands of imine group ,attributed to (C=N) (imine group) a stretching frequency is good evidence of this step of reaction. and appeared a new bands at(1680-1676) cm\(^{-1}\) due to of (C=O) in thiazine ring.

Antibacterial activity

The novel synthesized representative compounds were tested for their antibacterial activity against the following staphylococcus aureus, pseudomonas aureous, Escherichia coli. The preliminary screening of the investigated compounds were performed using the filter paper disc-diffusion method. The compounds were tested at concentration of 100µg/ml. the zone of inhibition was measured in mm (table1).

References


12. Tarik El-Sayed Ali and Azza M. El-Kazak. (2010) Synthesis and antimicrobial activity of some new 1,3-thiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles and 1,3-thiazines incorporating acridine and 1,2,3,4-tetrahydroacridine moieties. Eur. J. Chem 1, No 1:6-11


Table (1): Antibacterial activity of synthesized compounds 2a-6b

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Staphylococcus aureus</th>
<th>Pseudomonas aureous</th>
<th>Escherichia coli</th>
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<tbody>
<tr>
<td>2a</td>
<td>12</td>
<td>9</td>
<td>5</td>
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<tr>
<td>2b</td>
<td>7</td>
<td>12</td>
<td>11</td>
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<tr>
<td>3a</td>
<td>21</td>
<td>19</td>
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<td>3b</td>
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<td>17</td>
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<tr>
<td>4a</td>
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<td>11</td>
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<td>4b</td>
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<td>18</td>
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<tr>
<td>5a</td>
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<td>13</td>
<td>12</td>
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<tr>
<td>5b</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>6a</td>
<td>13</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>6b</td>
<td>14</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Scheme (2): The synthesis rout for Compounds (1-6 a, b)
تحضير وتشخيص ودراسة الفعالية المضادة للبكتيريا لبعض الخماسية- سباعية الحلقة الجديدة المرتبطة مع مركبات السلفون اماد

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استلم البحث في: 25 آذار 2014 ، قبل البحث في: 2 حزيران 2014

الخلاصة

هذا البحث يتضمن تحضير وتشخيص مركبات حلقة غير متجانسة خماسية وسباعية الحلقة من خلال المركب بنزين سلفون ايدرازنت. تم تفاعل قواعد شف (1a,b) في مجموعه السلفون اماد. تم تفاعل قواعد شف مع الأنيريدات الحلقاتية لتحضير كل من مشتقات الأوكسازين والثيازيدين (2,3,4a,b) ذات الحلقات السباعية. وتم تفاعل قواعد شف مع مركب (2) تحتوي على مشتقات ثيازيدين (6a,b) في الحلقة الخلوية. تم حضور مشتقات المركب ثيازوولدين (5a,b) من خلال تفاعل قواعد شف مع مركب (3). شاركت المركبات المحضرة من خلال بعض الطرق الكيميائية المختلفة مثل درجة الانصهار، وضفي الراكة تحت الحمراء، وضفي الزئبق النووي المغناطيسي، وجهاز تحليل العناصر الدقيقة. درست الفعالية البيولوجية للمركبات المحضرة ضد بعض أنواع البكتيريا إذا أظهرت الدراسة نتائج جيدة ضد بعض الأنواع من البكتيريا.

الكلمات المفتاحية: السلفون اماد، الأوكسازين، ثيازيدين، ثيازوولدين، قواعد شف، الفعالية المضادة للميكروبا.